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Epidemiology of transfusion-transmitted infections among multi-transfused patients in seven hospitals in Peru[1]

V.A. Laguna-Torres[a,*], J. Pérez-Bao[a], G. Chauca[a], M. Sovero[a], D. Blichtein[i], A. Chunga[b], W. Flores[b], A. Retamal[b], S. Mendoza[b], M. Cruz[c], Z. Monge[c], M. Lavalle[d], J. Gutiérrez[d], J. Málaga[e], E. Soto[e], N. Loayza[f], D. Bolívar[g], R. Reyna[g], C. Mendoza[h], M. Oré[h], J. González[i], M. Suárez[i], S.M. Montano[a], J.L. Sánchez[a,j], W. Sateren[j], C.T. Bautista[j], J.G. Olson[a], S. Xueref[k]

[a]*Naval Medical Research Center Detachment (NMRCD), Lima, Peru*
[b]*Hospital E Rebagliati, Lima,* [c]*Southeast National Hospital, Cusco,* [d]*Medical Naval Center, Lima,* [e]*Air Force Central Hospital, Lima,* [f]*National Hospital 2 de Mayo, Lima,* [g]*National Hospital Alberto Sabogal, Callao,* [h]*Central Military Hospital, Lima,* [i]*National Health Institute, Ministry of Health, Lima, Peru*
[j]*US Military HIV Research Program (USMHRP), Walter Reed Army Institute of Research,*
[k]*Pan-American Health Organization (PAHO), 525 23rd Street, NW, Washington, DC, USA*

Abstract

Background: Transfusion-transmitted infections (TTIs) constitute a major health problem worldwide where routine screening of blood or blood products is improperly done, and where non-medical injecting medications and/or drug use are prevalent. Prevalence and risk factors vary by geographic location and by the specific TTI (including HIV-1, HBV, HCV and HTLV-I). **Objective** To determine the prevalence and risk factors associated with TTIs among a sample of multi-transfused adult patients in Peru. **Study design:** A cross-sectional multi-center study was conducted across seven major hospitals in Peru from February 2003 to September 2004. Self-reported behavior information (medical procedures, number of sexual partners, and drug use history) was analyzed, along with a review of exposure history from hospital medical records. Prevalences were calculated by TTI for different exposures, along with unadjusted and adjusted odds ratios for infection risk. **Results** Overall, 192 (54.7%) of 351 multi-transfused patients were found infected with one or more TTIs. Number of transfusion units, years of transfusion history (6 or more), and number of treatment facilities (2 or more) were associated with HCV infection. Hemodialysis history was a common risk factor associated with HBV, HCV and HTLV-I infection. HIV infection was associated only with total number of transfusion units received. **Conclusions** High prevalences of HBV and HCV infection were found among Peruvian multi-transfused patients and were associated with a past history and number of blood transfusions, as well as with past hemodialysis procedures. TTIs continue to represent a significant public health problem in Peru. Continued vigilant attention to blood safety procedures, including universal screening and health care provider education, is recommended.

Keywords: Multi-transfused; HIV-1; HBV; HCV; HTLV-I; Epidemiology

1. Introduction

The worldwide distribution of hepatitis C virus (HCV) infection includes 170 million people who comprise approximately 3% of the global population (Bonkovsky and Mehta, 2001). Infection is most commonly acquired through blood transfusion from infected donors, unsafe therapeutic injection practices, and illegal injecting drug use (IDU) (Alter, 2004). In countries where HCV is common, such as Italy, Japan, Spain, Turkey and Taiwan, it is most prevalent in those over 40 years of age (Alter, 2004). However, in certain areas where it is hyperendemic, such as in Egypt's Nile Delta which has the highest HCV prevalence reported in the world, HCV infection occurs early in childhood and adolescence, reaching levels as high as 30% in the age group of 30–39 years (Alter, 2004, Abdel-Azia et al., 2000). In most developed countries, such as in the USA, most HCV infections can be accounted for by risk factors associated

* Corresponding author. Tel.: +51-1-561-2733; fax: +51-1-561-3042.
E-mail address: alaguna@nmrcd.med.navy.mil (V.A. Laguna-Torres).

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Human Use Statement: The study protocol was approved by the Peruvian National Institute of Health Institutional Review Board and by the Naval Medical Research Center Institutional Review Board (Protocol #NMRCD.2002.0018) in compliance with all Federal regulations governing the protection of human subjects.

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with percutaneous (mainly IDU) and mucosal exposures to blood (Alter, 2004, Catalina and Navarro, 2000). In countries where screening is performed on all blood donors using a multigenic sensitive test, the annual rates of HCV infection and other transfusion-transmitted infections (TTIs) have dropped markedly (Catalina and Navarro, 2000).

In Peru, hepatitis B (HBV) and hepatitis C (HCV) remain significant public health problems (Vildosola et al., 1990, Casey et al., 1996, Sánchez et al., 2000). Peru has intermediate endemicity for HBV with major variations in prevalence across many regions of the country. Highest prevalence is found in mountainous central Andean cities and lowest in the coastal regions (Chang et al., 1997, Ministerio de Salud del Perú, 2000, Cabezas, 2002). In 1989, HCV prevalence was found to be less than 1% among 123 people who had been working in areas of high risk of HCV infection. Cross-sectional studies have identified potential iatrogenic infection (via contaminated injections) (Mejía Aliaga, 1993) as well as a high HCV prevalence associated with procedures like hemodialysis, and in patients with hemophilia (Sánchez et al., 2000). Risk factors for HBV infection have been studied in several Peruvian hospitals (Valladares et al., 1989, Mejía Aliaga, 1993) with varying results. Female commercial sex work has also been found to be associated with HBV transmission in several Peruvian cities in the past (Colichón et al., 1990).

The Expanded Program for Immunization Program (PAI, initials in Spanish) of the Peruvian Ministry of Health (MoH) initiated a pilot immunization program against HBV in two hyper-endemic areas: Abancay in 1991 and Huanta in 1994 (Cabezas et al., 2000). PAI carried out large-scale HBV vaccination efforts in other endemic areas of Peru (Ministerio de Salud del Perú, 2000).

Another blood-borne infection of importance in Peru is that caused by human T-cell lymphotropic virus type I (HTLV-I), a virus associated with leukemia and lymphoma initially identified in 1980 (Poiesz et al., 1980). Infection with HTLV-I has been described in individuals born in the "Peruvian Andean Trapeze" region (Andean Departments of Ayacucho, Abancay and Cusco) (Zurita et al., 1997) and was associated with tropical spastic paraparesis (TSP-HAM) (Gotuzzo et al., 1996). Control of HTLV-I by screening in blood banks has succeeded in blocking the spread of the virus in Japan (Osame et al., 1990), and universal donor screening of blood products in blood banks has helped to contain the spread of this virus in Peru.

2. Materials and methods

The study objectives were to determine the prevalence and risk factors associated with TTIs (HIV-1, HBV, HCV and HTLV-I) among multi-transfused patients with bleeding disorders and/or those patients undergoing chronic hemodialysis.

2.1 Study population

Between February 2003 and September 2004, a multicenter study was conducted among seven major hospitals in Peru, including 5 in the Lima metropolitan area, one in the port city of Callao, and one in the mountain region city of Cusco. Three of the participating hospitals were from the Social Security System of Peru (EsSalud), three were National Military Hospitals, and one was from the Peruvian Ministry of Health. Collaborative agreements were pursued with each hospital center, with the appropriate funding support, guidance and technical consultative assistance of the Pan American Health Organization (PAHO).

A sample size of 500 was chosen assuming that the prevalence of TTI was 50% and allowing for a refusal frequency of 20%.

Inclusion criteria

Subjects aged 18 years or older with a history of transfusion of a total of at least ten units of allogeneic blood or blood components (i.e. whole blood, plasma, red blood cells or platelets), received on at least two different occasions and/or with a history of at least three hemodialysis sessions were enrolled. Study subjects met at least one of five criteria: (a) hemophilia or another coagulation disorder, (b) hemodialysis, (c) sickle-cell anemia or thalassemia, (d) acute blood loss, or (e) oncologic or hematological disease.

Exclusion criteria

Subjects were excluded on the following criteria: under the age of 18 years, disseminated ecchymosis and/or bruises, any intravenous chemotherapy or active bleeding within 7 days prior to recruitment, platelet count $<20\,000/mm^3$, hemoglobin <8 g/dl, or previous documented medical or laboratory record evidence of HBV or HCV infection prior to the first lifetime transfusion.

2.2 Confidentiality

A unique identifier (study code) was placed on the informed consent document, on the survey form, and on the blood sample tube. No names, clinical record numbers or any other personal identifiers were associated with participants' samples received and processed at the NMRCD-Lima laboratory. A 7-digit code system was devised by PAHO officials, wherein the first 3 letters described the country and the last 4 described the specific subject. In Peru we used PER and the numbers between 1000 and 9999. The local investigator at each site was the only person who had access to both the name and ID number for participants at each site.

2.3 Data collection and management

After patients provided written informed consent, a blood sample was collected and a questionnaire administered to collect self-reported data on demographics, medical history, and high-risk behaviors. The analyses included

data such as the date of initial exposure (whether prior to the enactment of national law requiring screening of all blood products), length of time and number of locations in which exposures occurred, actual number of exposures, and additional behaviors (use of cocaine, partners, alcohol) or procedures which patients may have undergone, such as dental extractions, endoscopy, and intravenous therapy administered by unlicensed healthcare providers. A review of the subject's medical record was conducted to confirm the specific condition and number of transfusions received. Study forms (clinical and epidemiologic questionnaire information and laboratory data) were double-entered into a master database that was developed by the NMRCD-Lima data management center and not shared with participating hospitals to prevent violation of subjects' confidentiality.

2.4 Laboratory analyses

Blood samples were collected in an anticoagulated (EDTA-containing) tube, and 3 plasma aliquots of 1.8 ml each were obtained from each subject. Testing was completed using one aliquot and the remaining samples were stored at −70°C at NMRCD-Lima for future PAHO studies. Screening assays included anti-HCV testing (HCV EIA 4.0X 3rd generation UBI®), anti-HIV-1/2 testing (HIV Uni-Form II Ag/Ab Vironostika® and Bio-Rad Genscreen® PLUS HIV Ag-Ab) anti-HTLV-I/II testing (ELISA Vironostika® HTLV I/II) and hepatitis B core antibodies (anti-HBc uniform Hepanostika®). In addition, samples were tested for hepatitis B surface antigen (ELISA Hepanostika® HBsAg Uni-Form II third generation). HBsAg-positive samples were confirmed by neutralization test (Murex HBsAg Confirmatory Version – Abbott®). Repeatedly-reactive samples for HIV-1 or HTLV-I/II screen tests were confirmed by immunoblot techniques (New Lab Blot I Bio-Rad® and HTLV-I/II (HTLV blot 2.4 Genelabs Diagnostic®). Readers and washers from DYNEX ®Technologies were used for all tests.

2.5 Statistical analysis

Chi-square and Fisher's exact test were used to compare proportions. Analysis was performed using quartiles for specific variables to determine their relationship to the most common infection. Odds ratios (OR) and adjusted OR (AOR) were calculated by logistic regression analysis with robust standard errors to adjust for possible correlation within multi-centers, as well as associated 95% confidence interval (CI). Risk factors that were found to be significant in univariate analysis were entered into a forward stepwise multivariate logistic regression analysis to identify independent potential risk factors associated with TTIs. All p-values were two-sided, $p < 0.05$ was considered to be statistically significant. All analyses were carried out using SPSS v. 10 (SPSS Corporation, Chicago, IL) and Stata v. 8.0 (Stata Corporation, College Station, TX).

3. Results

3.1 General findings

A total of 351 multi-transfused patients were enrolled in this multicenter study, 228 (65%) men and 123 (36%) women (Table 1). The patients ranged in age from 18 to 92 years with a mean age of 45 yrs (SD 19.1 years). This total included 154 patients from the Hospital E. Rebagliati, 42 from the Southeast National Hospital, Cusco, 39 from the National Hospital "Alberto Sabogal", Callao, 60 from the Hospital 2 de Mayo, 25 from the Medical Naval Center (CEMENA), 21 from the Peruvian Air Force Central Hospital (HCFAP) and 10 from the Central Military Hospital (HMC). Of those studied, 24% were diagnosed with hemophilia, 19% had undergone hemodialysis, 26% had acute bleeding, and 27% had oncologic or hematological disease. More than one diagnostic inclusion category was found in 18 (5%) patients.

The most common blood products received were red blood cells and plasma, which were received by 279 (79%) and 235 (67%) patients, respectively. However, subjects were exposed to an array of blood products: 288 (82%) had received between two and five types of blood components (i.e. whole blood, plasma, red blood cells, platelets, or cryoprecipitate), although only 28 (8%) were ever transfused with whole blood and 63 (18%) had had only one type of blood component in their lifetime. A small percentage of patients had tattoos or body piercing (5.4% and 12.5%, respectively) and only 3 (0.9%) reported any past history of injecting drug use (IDU). One half (50.3%) of study participants reported two or more sexual partners in their lifetime, while 12.5% denied any sexual partner at any time.

3.2 Prevalence of TTIs

Overall, 192 (54.7 %) of 351 multi-transfused patients were infected with one or more TTI. Evidence of prior HCV infection was found in 116 (33.0%), prior HBV infection in 140 (39.9%), HIV-1 infection in 5 (1.4%), and HTLV-I infection in 11 (3.1%) of study subjects (Table 1). An increase in HTLV-I prevalence was observed with increasing age (>43 years). No specific seroprevalence trends were observed for educational level, a surrogate marker for socioeconomic status. Interestingly, increasing trends in HBV and HTLV-I prevalence were observed with an increase in the number of lifetime sexual partners, although this finding was not statistically significant.

Significantly higher HCV prevalences were detected among hemophiliacs (56.6%) and patients on hemodialysis (61.5%). HIV-1 infection was found to be more prevalent among patients with hemophilia (4.8%), while HBV (60.0%) and HTLV-I (9.2%) were more common among hemodialyzed patients (Figure 1).

Volunteers from the three types of health facilities (military, social security system, and MoH) differed from each other in educational achievement. Overall 36% of

Table 1
Demographic characteristics and prevalence of transfusion-transmitted infections (TTIs) among 351 multi-transfused patients, Peru, 2003–2004

Group	No of participants		HCV		HBV		HIV-1		HTLV-I	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	351	100	116	33 0	140	39 9	5	1 4	11	3 1
By gender										
Female	123	35 0	34	27 6	47	38 2	–	–	4	3 3
Male	228	65 0	82	36 0	93	40 8	5	2 2	7	3 1
By age group										
18–28	87	24 8	35	40 2	33	37 9	3	3 4	1	1 1
29–43	87	24 8	29	33 3	35	40 2	–	–	1	1 1
44–59	87	24 8	31	35 6	35	40 2	2	2 3	3	3 4
60	90	25 6	21	23 3	37	41 1	–	–	6	6 7
By educational level										
Less than High school	57	16 3	16	28 8	27	47 4	0	0 0	1	1 8
High school	127	36 2	44	34 6	54	42 5	3	2 4	7	5 5
Technical	62	17 7	17	27 4	20	32 2	1	1 6	2	3 2
College	105	29 9	39	37 1	39	37 1	1	1 0	1	1 0
By past behavioral/medical history [a]										
Presence of tattoos	19	5 4	7	36 8	8	42 1	1	5 3	1	5 3
Presence of body piercing	44	12 5	16	36 4	15	34 1	1	2 3	1	2 3
Acupuncture treatment	24	6 8	9	37 5	12	50	–	–	–	–
Intravenous treatment by non-medical professional	22	6 3	5	22 7	5	22 7	–	–	1	4 5
Number of lifetime sexual partners										
0	44	12 5	20	45 5	17	38 6	1	2 3	–	–
1	92	26 2	30	32 6	32	34 8	–	–	2	2 2
2	176	50 1	60	34 1	78	44 3	3	1 7	8	4 5
No answer	39	11 1	5	13 2	13	33 3	1	2 6	1	2 6
Transplantation	28	8 0	13	46 4	11	39 3	–	–	1	3 6
Endoscopy	166	47 3	66	39 8	70	42 2	2	1 2	7	4 2
Dental procedure involving tooth extraction	287	81 8	93	32 4	114	39 7	4	1 4	10	3 5

[a] Information obtained through patient self-report

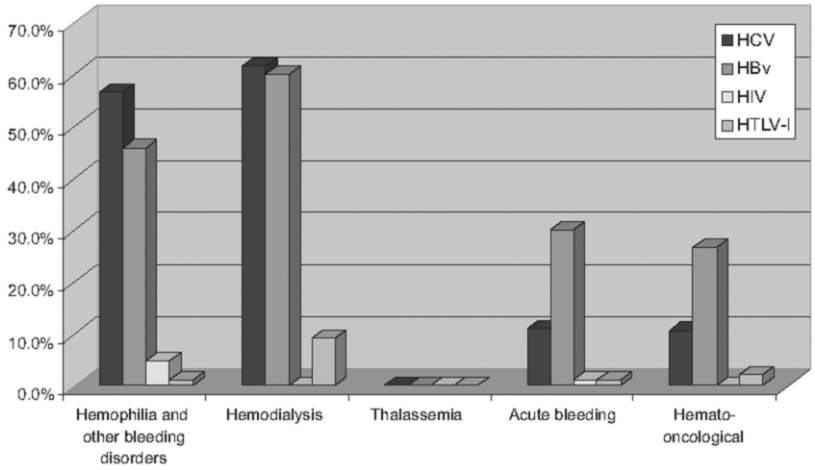

Fig 1 Prevalence of TTI by hematological diagnosis in 351 multi-transfused patients, Peru 2003–2004

Table 2
Multiple logistic regression analysis of risk factors for TTIs among multi-transfused patients, Peru 2003–2004[a]

Feature	AOR	(95% CI)	*p*-value
HCV			
Total number of transfusion units received (Q4>53)	2 5	(1 8–3 5)	<0 001
Number of transfusion events in lifetime (Q4>24)	2 6	(1 2–5 5)	0 015
Number of treatment facilities (>2)	3 5	(2 8–5 0)	<0 001
Number of years of exposure to transfusions (Q4>5)	5 6	(3 6–8 8)	<0 001
Hemodialysis (yes)	6 5	(5 0–8 6)	<0 001
Number of facilities of hemodialysis exposition (>2)	4 0	(1 3–12 5)	0 015
Endoscopy (yes)	2 5	(1 5–3 9)	<0 001
Hemophilia (yes)	4 1	(2 1–6 1)	<0 001
HBV			
Total number of transfusions units received (Q4>53)	2 17	(1 21–3 9)	0 009
Number of transfusions events in lifetime (Q4>24)	2 01	(0 9–4 0)	0 051
Number of treatment facilities (>2)	1 6	(1 4–1 8)	<0 001
Number of years of exposure to transfusions (Q4>5)	2 7	(2 1–3 5)	<0 001
Hemodialysis (yes)	2 9	(1 3–6 5)	0 010
HIV			
Total number of transfusion units received (Q4>53)	8 7	(5 4–14 2)	<0 001
Number of sexual partners (>4)	2 7	(0 9–7 1)	0 051
HTLV-I			
Number of treatment facilities (>2)	2 1	(1 1–4 0)	0 027
Hemodialysis (yes)	7 1	(2 5–20 4)	<0 001

[a] TTIs, Transfusion-transmitted infections, HCV, hepatitis C virus, HBV, hepatitis B virus, HIV-1, human immunodeficiency virus type 1, HTLV-I, human T-cell lymphotropic virus type I, Q4, fourth quartile, AOR, adjusted odds ratio by age, gender and educational level, 95% CI, 95% confidence interval, exposure category is in parenthesis

the volunteers included in this study had high-school level degrees. While 30% of volunteers overall reported receiving a university degree, among the MoH volunteers there were no persons with a university degree. However, no relationship between education level and TTI infection was observed.

3 3 Risk factors analyses

Potential TTI risk factors associated with specific exposures and diagnoses are shown in Table 2. Hemodialysis represented the single most important risk factor associated with TTIs. Hemodialysis was associated with an increase in risk of approximately 6.5 times for HCV, 2.9 times for HBV and 7.1 times for HTLV-I. In addition, HCV infection was associated with a number of other medical procedures including the number of previous blood transfusion events (AOR = 2.6 for 24 or more), total number of transfusions received (AOR = 2.5 for 54 or more lifetime units), number of treatment facilities visited (AOR = 3.5 for 3 or more), number of years receiving transfusions (AOR = 5.6 for 6 or more years), number of facilities of hemodialysis exposition (AOR = 4.0 for 3 or more), history of a previous endoscopic procedure (AOR = 2.5) and history of hemophilia (AOR = 4.1).

HIV infection was associated with total number of transfusion units received (AOR = 8.7 for 54 or more lifetime units) and with a greater number of lifetime sexual partners (AOR = 2.7 for 5 or more). HTLV-I infection was found to be associated with hemodialysis as well as with number of different treatment facilities utilized (AOR = 2.1 for 3 or more). Many significant associations found in univariate analysis were also found to be significant in multiple logistic regression analysis.

After adjustment for confounding using forward stepwise logistic regression, we found that hemodialysis history continued to be a significant factor associated with all TTIs except HIV (Table 3). Additionally, a greater number of lifetime transfusion units received (54 or more) was also associated with an increased risk for HCV and HIV infections. No statistically significant associations were observed with body piercing history or tattoos and any TTI. Likewise, there were no associations observed

Table 3
Table III Forward stepwise multivariate logistic regression analysis of risk factors for TTIs among multi-transfused patients, Peru 2003–2004[a]

Feature	AOR	(95% CI)	p-value
HCV			
Total number of transfusion units received (Q4>53)	2 7	(1 0–7 4)	0 049
Number of treatment facilities (>2)	2 4	(1 9–2 9)	<0 001
Number of years of exposure to transfusions (Q4>5)	5 4	(4 2–7 0)	<0 001
Hemodialysis (yes)	13 1	(5 3–32 2)	<0 001
HBV			
Total number of transfusion units received (Q4>53)	2 4	(1 1–5 1)	0 028
Number of years of exposure to transfusions (Q4>5)	2 3	(1 2–4 2)	0 008
Hemodialysis (yes)	4 1	(2 5–6 7)	<0 001
HIV			
Total number of transfusion units received (Q4>53)	10 8	(5 4–21 9)	<0 001
HTLV-I			
Hemodialysis (yes)	7 1	(2 1–24 4)	0 002

[a] TTIs, Transfusion-transmitted infections, HCV, hepatitis C virus, HBV, hepatitis B virus, HIV-1, human immunodeficiency virus type 1, HTLV-I, human T-cell lymphotropic virus type I, Q4, fourth quartile, AOR, adjusted odds ratio by age, 95% CI, 95% confidence interval, exposure category is in parenthesis

for acupuncture treatment, organ transplantation or dental procedures involving tooth extraction.

4. Discussion

This study provides information that will assist in developing intervention guidelines to reduce the risk of acquiring TTIs, which continue to be a significant public health problem in Peru. The risk for TTIs (such as HIV, HBV, HCV and Chagas disease) has been previously reported to be lower in Peru than in other countries of the region (Schmunis et al., 1998). Overall, high prevalence of infection was found for HBV (39% for anti-HBc and 6.8% for HBsAg) and HCV (33%). By comparison much lower prevalences of infections were found for HIV (1.4%) and HTLV-I (3.1%).

The high prevalence of HCV observed among hemophiliac and hemodyalized patients could reflect the limitations for continued blood screening as well as safe practices for hemodialysis procedures in Peru. Continued attention to the universal screening of blood products for TTIs as well as a more scientifically-sound and rational approach to avoiding paid blood donors, as well as a more thorough screening and selection of potential blood donors, is necessary to limit the number and rate of TTIs in Peru in the future (Schmunis et al., 1998, Schreiber et al., 1996).

No relationship between educational level and the TTI infection was observed. The number of years of transfusion history, as well as use of multiple different medical treatment facilities to provide these services (implying a lack of biosafety precautions by certain healthcare providers/institutions) was related to increased frequency of infections, especially for HCV.

Although mandatory blood screening was established in Peru in 1996 (Ministerio de Salud del Perú, 1996), each of the hospitals included in this study started screening at different times. Our results show a significant association between the number of years (6 or more) of blood exposure prior to the introduction of mandatory blood screening to HCV infection.

There was no statistically significant difference in TTI prevalence between individuals who received inactivated concentrated factor and those who received other blood components. Among hemophilic patients specifically, no protective effect was observed with the use of concentrated factor. In Peru, the lyophilized concentrated factor is provided mainly from the USA and freely distributed in the main medical centers such as the Edgardo Rebagliati Martins (EsSalud) and the 2 de Mayo Hospital (MoH), both hospitals in Lima. Hemophiliac patients from rural provinces have more serious difficulties obtaining this factor, especially if they do not belong to the social security system of Peru.

It is noteworthy that, contrary to findings in other published studies (Sánchez et al., 2000, Haley and Fisher, 2001, Sulkowski et al., 2002), we found no significant associations for any of the TTIs with other medical or dental types of exposure or for exposures to non-medical parenteral procedures, such as therapeutic injections, acupuncture, ear

piercing or tattooing. It is possible, however, that since only a minority of study subjects (8%) reported these exposures, the power of our study may not have been sufficient to detect minor differences in risk. In addition, we found no associations between level of alcohol or intranasal cocaine consumption with any TTIs.

Only 75 participants had received the hepatitis B vaccine. No statistically significant difference in the presence of surface antigen to hepatitis B was observed between vaccinated and non-vaccinated patients. HBV infection was confirmed by neutralization test in 24 patients (6.8%) and the route of infection was unknown. Conclusions from this observation cannot be made considering other variables such as poor vaccine response, or low antibody protective titers (less than 10 IU/ml). The latter has been reported in nearly 60% of vaccinated patients 9 and 11 years post-vaccine (Mahoney, 1999).

It should be pointed out that the characteristics of the subjects included in this study differ depending on what their background is and whether they obtain their medical services from military, social security system or MoH institutions. This is evident by the gender and educational distribution of the three populations. Overall, 36% of the volunteers included in this study had high-school level degrees and 30% had received a university degree. However, among patients seen at MoH hospitals, there were no persons with a university degree. In addition, the accessibility to transplant services and hemodialysis procedures was significantly less in the case of MoH-treated subjects. Study volunteers from the MoH had to personally pay for these medical procedures, individuals in the social security system have free access to these same procedures. Most of the volunteers (83%) were from the military and the social security system (EsSalud). Only 60 volunteers were from 2 de Mayo Hospital from the Ministry of Health of Peru (MoH).

A major limitation of our study is that it included only adult participants, many of whom (i.e., hemophiliacs) had received transfusions for many years from several hospitals. Prior transfusion history may have been underestimated by relying on patients' self-reporting and a review of medical records from only specific facilities. The most precise information available was from the five- or six-year period prior to the date of the blood sample collection.

Finally, this study does not support the hypothesis that patients who received some blood components such cryo-precipitate sustained lower risk for TTIs (especially HBV and HCV). Although strong national policies requiring the routine screening of blood and blood components were established by the government and public health authorities in Peru in the early 1990s (PAHO, 1995), it is necessary to continue to emphasize blood safety and universal precautions for all healthcare providers. In addition, there is an acute need to ensure access to clean, non-reusable needles/syringes, to ensure continuing screening and follow-up of blood donors, and to counsel patients at high risk, given that infection is possible (CDC, 1991, 1998). Infected individuals need to be provided with timely and effective advice on how to prevent transmitting their infections to others at risk.

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